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| EXAMINER | |
|---|---|
| HIRIYANNA, KELAGINAMANE T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/531,855 | BERKEL ET AL. | |
| | Examiner | Art Unit | |
| | KELAGINAMANE T. HIRIYANNA | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,13 and 16-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response filed on 07/07/2008 in response to office action mailed on 02/07/2008 has been acknowledged.

Claims 1-10, 13, 16, and 21 are amended.

Claim 11 is canceled.

Claims 12, 14-15 were previously cancelled.

*Claims* 1-10, 13 and 16-22 *are pending and are examined in this office action.*

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is* ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Withdrawn: Rejection of claims 1-10, and 13 under 35 USC 102 (b) as being anticipated by Wolf et al., (2001, Protein Expression and Purification 22:414-421; art of record) for the reasons of record as set forth in the office action mailed on 02/07/2008 is hereby withdrawn in view of Applicants arguments, amendments to claims and in view of the 35 USC 103 rejections below.

Withdrawn: Rejections of Claims 1-11 and 13 under 35 U.S.C. 112, first paragraph, as failing to comply with written description requirement for the reasons of record as set forth in the office action mailed on 02/07/2008 is hereby withdrawn in view of Applicants arguments, amendments to claims and in view of the submissions of prior art in support for the broad claims.

Withdrawn: Objections to claims 2-11 made for the reasons of record as set forth in the office action mailed on 02/07/2008 is hereby withdrawn in view of Applicants appropriate amendments to claims.

## Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-11, 13 and 16-22 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant human C1 inhibitor that is changed in its circulatory half-life by a O-linked carbohydrate modification in vitro using a O-linked carbohydrate modifying enzymes ST3Gal I and/or ST3Gal III, is not enabled for any O-linked carbohydrate modifying enzymes for increasing the circulatory half life of said human recombinant C1 inhibitor or for changing the circulatory half-life of a human C1 inhibitor in vivo as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. “Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through ‘’undue experimentation” in order to practice the invention.

***Nature of the invention and the breadth of the claims:***

The scope of invention as claimed encompasses compositions or products of a recombinant human C1 inhibitor that is modified in its o-linked glycosylation site using any modifying enzyme of an O-linked carbohydrate.

However applicant does not disclose representative enabled examples of any broadly claimed protein O-glycosylation modifying enzymes other than ST3Gal I and ST3Gal III for increasing the half-life of C1 inhibitor in vivo in any cultured cell. In the absence of representative number of enabled examples several subgenus of enzymes encompassed by the claim it would require undue experimentation to practice the invention in its full scope.

***The level of one of ordinary skill in the Art at the Time of Invention:*** The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

***Guidance of the Specification, Existence of Working Examples, State of the Art and the Predictability of the Art*:** With respect to invention instant specification only provides guidance and/or evidences regarding use of an a method of using an C1 inhibitor (rhC1INH) that is scialylated on O-linked carbohydrate moieties in vitro and intravenously injecting the same to provide C1 inhibitor with an increased half-life in plasma circulation. At the best the specification only teaches regarding modifying a recombinant human CI inhibitor (rhC1INH) with O-linked carbohydrate modifying enzymes ST3Gal I, ST3Gal III. Further the specification does not teach any other O-linked carbohydrate modifying enzymes other than ST3Gal I and ST3Gal III that modify to increase the circulatory half life of the human C1 inhibitor. Given the lack of predictability in the prior art regarding the functions of various carbohydrates introduced or removed by a glycosylation modifying enzymes, the central question how glycosylation contributes to the glycoprotein structure and function is not entirely clear (Wang et al., 1996, Biochemistry 35:7929-7307, entire article, abstract; p.7299, col.2 bridging p.7300). Different glycosylation moieties introduced by different enzymes may cause various specific effects such as intracellular traffic and localization of protein,

modification of immunological properties and other properties apart from increasing circulatory half-life of a protein or tability of the proteins. Thus with the upredictability of the art regarding the role of glycosylations coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the invention as claimed i.e., using any O-linked carbohydrate modifying enzyme to change the stability of the protein. Further the one of skill in the art would not predict what kind of change is brought about by different enzymes.

***Amount of experimentation necessary:*** These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully predict a priori the specific effects of modifying O-glycosylation of C1 inhibitor by different carbohydrate modifying enzyme. One of skill in the art have to experiment with different glycosylating deglycosylating enzymes and those with specificity for different sugar moieties and test the so modified human C1 inhibitor samples for stability in the circulation in live animals or animals. However, one of skill in the art would be confused if these introduced modifications in O-linked sugars bring in any other effects on the modified protein in terms of its specificity, localization or immune reactions etc. Accordingly, in view of the lack of teachings in the art or guidance provided by the specification with regard to an enablement of sufficient number of examples broadly claimed glycosylation modifying enzymes as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention.

**In Response to Arguments of 07/07/2008:**

Applicant amends claims to reflect in vivo modifications restricted to cultured cell lines. Applicant argues therefore concerns over the enablement of the scope of the claim encompassing in vivo modulation of O-linked glycosylation in proteins is overcome because the amended claims restrict the scope of in vivo modulation to cultured cells only.

Applicants' arguments are however, found not persuasive because firstly the primary Claim 16 as amended still encompasses in its breadth modulation of O-linked glycosylation of C1 protein using broad genus O-glycosylation modifiying enzymes.

In the absence of an enabled example and/or a representative number of enabled examples in the specification regarding specificity of modulation by representative number of species of various sub genus of O-linked glycosylation enzymes used for modifying a therapeutic protein such as C1 inhibitor or other protein one of ordinary skill in the art would conclude that the invention as instantly claimed is unpredictable and 'undue'. Hence the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 13 and 16-22 are rejected under 35 USC 103 (a) as being unpatentable over Paulson et al (1998, WO 98/31826), Shoenberger et al (1992, FEBS 314: 430-434), Wolf et al., (2001, protein expression and purification 22:414-421) and in view of Glaser et al (WO 92/03149) and Lamark et al (2001, Protein expression and Purification 22:349-358; art of record).

The above claims are directed to a recombinant human C1-inhibitor that is changed with regard to its plasma circulatory half-life by modification of an O-linked carbohydrate by an O-linked carbohydrate modifying enzyme in vitro or in vivo in a cultured cell.

Regarding claims 1-6 and Paulson teaches increasing plasma circulatory half life of therapeutic proteins including C proteins and other proteins that have been produced recombinant method and by modifying both N- and O-glycosylation moieties (Abstract, p.2, 3rd paragraph) by scialylation (p.2, 4th paragraph brdging p.3). Regarding claims 7-9 Paulson teaches use of one or more enzymes including ST3 gal I, ST3 Gal III etc., (p.3, 2 and 3rd paragraph and p.18, Examples). Regarding claim 10-12 Paulson teaches

various recombinant glycoproteins that are modified in vitro sialylation (p.7, 2nd, 3rd and 4th paragraph bridging p.8, and p.25) and pathways to obtain a recombinant inhibitor (rC1INH) for clinical evaluation (p.420, col.1). Reasons to believe otherwise Paulson's recombinant C1 inhibitor preparation with its modified O-glycosylation sites have its circulatory half-life changed.

Schoenberger teaches C1 inhibitor and recombinant C1 inhibitor and the characterization of the carbohydrate moieties and removal of sialic acids from native molecules (p.431, col.2) and the characterization of desialylated C1-inhibitor (p.432, 2nd paragraph) and further considered to see whether the carbohydrate part of C-1 inhibitor influences the inhibition mechanism of the inhibitor (p.433, col.2, 2nd paragraph)

Wolf teaches regarding production and purification of recombinant C1 inhibitor and the various glycosylations levels of C1INH (p.415, col.1, 2nd paragraph). Wolf further teaches the differences between native and recombinant molecules in terms of their glycosylation and the importance of reduced O-glycosyaltion in hereditary diseases involving (p.419, col.2, 2nd paragraph). He further indicates engineered glycosylation pathways to obtain recombinant inhibitor (rC1INH) for clinical evaluation (p.420, col.1).

Glaser teaches a method of treating a thrombotic disease using therapeutic proteins like C protein that are modified in sugar residues of the O-linked glycosylation domain and encompassing modification by deletion of sugar moieties enzymatically (p.4, 1st paragraph).

Lamark teaches regarding expressing an active recombinant human C-1 inhibitor in Escherichia coli (entire article; abstract). Lamark further observes that glycosylation of C1 inhibitor is not critical or important. (Abstract).

Thus it would have been obvious for one of ordinary skill in the art to incorporate into compositions and methods of using human C1 inhibitor incorporate a method of modifying scialylation or descialylation at O-linked glycosylation sites as taught by Paulson, Wolf, Glaser and Lamark and use the O-glycosylation site modified human C1

inhibitors for treating subject in need. One skilled in the art would be motivated to do so for treating a disease related to reduced C1 inhibitory activity by providing C1 protein that has been recombinantly produced and/or modified to increase its plasma circulatory half life by scialylating or desialylating O-linked carbohydrate moieties because the art teaches it is routine to produce a recombinant human C-1 inhibitor with changed modification status of O-linked carbohydrates (as compared to that of normally expressed in humans) and use them for therapeutic purposes.

Thus, the claimed invention was *prima facie* obvious.

**In Response to Arguments of 07/07/2008:**

Applicant argues that Paulsosn's reference is not relevant because he does not do not expressly teach the importance of O-linked glyosylations in changing circulatory half-life of the C1 inhibitor even though Paulson used recombinant C1 inhibitors with changed glycosylation modification status.

The Applicants arguments are however found not persuasive the C1 inhibitor with a modification (generic modification as calimed ) in its O-glycosylation is the same irrespective of the steps of processing to prepare it. The cited prior art thus clearly anticipates the invention as claimed because the product namely " a recombinant C1 inhibitor" are physically the same as the prior art product and must have the same properties unless shown otherwise. "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)".

***Conclusion:***

No claim allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/

Primary Examiner, Art Unit 1633